REMARKS

Status of the Application and Claims

With entry of this amendment, Applicants request reconsideration and allowance of pending claims 1-16 and 18-21. Claims 1-21 are stated as rejected. Applicants have amended the specification at the request of the Office and further amended claims 1-16 and 18-21. No new matter was added by way of these amendments.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Office rejected claims 1-21 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter the applicants regards as its invention. Office Action, 06/24/03 at 3, ¶ 6.

Specifically, the Office rejected claim 1 as unclear as to the meaning of the first and second parts of the disclosed kit. *Id.* Moreover, the Office states that it is unclear "whether this antibody [of the second part] is the specific binding partner of the drug conjugate or of some undisclosed drug." *Id.* Lastly, the Office rejects claim 1 as unclear as to whether the "antibody is labeled with gold material and latex particles as indicated by the alternative language of the claim." *Id.* The Applicants amend claim 1 to further clarify its meaning and respectfully request the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Claims 5-7, 9, 12, 15-17 and 19-21 are rejected as indefinite under 35 U.S.C. § 112, second paragraph. *Id.* at 3-4, ¶ 7. Applicants respectfully submit herein amended claims 5-7, 9, 12, 15-16 and 19-21 to remove any improper dependent claim form, and, thus, request this rejection be withdrawn. Claim 17 is canceled by this amendment.

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The Office additionally rejected claims 2 and 6 under 35 U.S.C. § 112, second paragraph, for reciting the limitation "said drug." *Id.* at 4, ¶ 8. Applicants obviate this rejection by submitting amended claims 2 and 6. Accordingly this rejection is overcome.

The Office rejected claim 9 under 35 U.S.C. § 112, second paragraph, as "unclear what the interior is coated with, i.e., is it antibodies or something else." *Id.*, ¶ 9. The Applicants respectfully submit amended claim 9 to better clarify its meaning. It is believed this rejection is overcome.

Claim 12 was rejected by the Office as indefinite under 35 U.S.C. § 112, second paragraph, for use of the term "maximum binding." *Id.* at 4, ¶ 10. Applicants respectfully submit amended claim 12; the rejection is now moot.

The Office rejected claims 11 and 13 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter the applicants regards as its invention. *Id.* at 4-5, ¶ 11. Specifically, the Office states that the use of the trademark NUNC-IMMUNO ™ STICK is indefinite and cannot identify or describe the goods associated with the trademark or name. *Id.* at 5. The Applicants respectfully traverse. The shape, to which claim 11 is drawn, and material, to which claim 13 is drawn, of a NUNC-IMMUNO ™ STICK is well known by one skilled in the art and thus satisfies the requirement under § 112, second paragraph. Moreover, as discussed by the Office in its official action at page 12, ¶ 15, the Applicants provided with this application a 1997 reference by P. Esser entitled, "Nunc-Immuno ™ Stick Methods." *See* form PTO-892, Paper No. 13, Notice of References Cited. According to the Office, "Esser teaches NUNC-IMMUNO ™ STICK." Office Action, 06/24/03 at 12, ¶ 15. Further, Esser provides Figures 1 and 2, both of which clearly show the

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shape of the NUNC-IMMUNO ™ STICK, as known by those skilled in the art. As requested by the Office at page 2, ¶ 4, each use of the trademark "NUNC-IMMUNO ™ STICK" has been capitalized to protect the value of the trademark. The applicants respectfully request this rejection be withdrawn.

Lastly, the Office rejected claims 16-21 as being incomplete for omitting essential steps under 35 U.S.C. § 112, second paragraph. *Id.* at 5-6, ¶ 12. Applicants submit amended claims 16 and 18-21 to better clarify the meaning of its invention. Applicants respectively assert this rejection is now moot. As noted previously, claim 17 has been canceled.

Rejections Under 35 U.S.C. § 103(a)

The Office rejected claims 1-3, 5-10, 12 and 14-21 under 35 U.S.C. § 103(a) as being "unpatentable over Jehanli et al., (1996) and Baker et al., in view of Cole et al., (US Patent 4,589,612)." *Id* at 6, ¶ 13.

According to the Office, it would have been obvious to a person of ordinary skill in the art "to modify the medical kit for qualitative or quantitative determination of a drug in a biological fluid comprising a first part coated with a drug conjugate and a second part that contains a[n] enzyme labeled antibody and is adapted for receiving said fluid as taught by Jehanli et al., wherein no more than routine skill would have been required to incorporate the lisinopril drug conjugate and gold labeled antibody of Baker et al., and Cole et al." *Id* at 9. Applicants respectfully traverse.

As set forth in M.P.E.P. § 2143.01, in order to establish a *prima facie* case of obviousness, the Office must meet three criteria. "First, there must be some suggestion or incentive, either in the references themselves or in the knowledge generally available to one of

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ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." M.P.E.P. § 2143.01 and cases cited therein.

As explained below, the Office has failed to establish a *prima facie* case of obviousness because one of skill in the art would not be motivated to combine the teachings of Jehanli et al., Baker et al., and Cole et al. Further, the skilled artisan would not reasonably expect to succeed in achieving a medical kit (and method) that provides ease of use, sensitivity, rapid results, and stability with temperature fluctuations. Finally, the references, individually or when combined, do not teach or suggest all the claimed limitations. At a minimum, the references do not teach or suggest the use of a kit that provides results within 60 minutes, do not teach or suggest the use of a kit with stability for home use by a patient, do not teach or suggest the use of a first and second part as disclosed by the Applicants, and do not teach or suggest the use of lisinopril in a kit as disclosed by the Applicant.

The primary reference, Jehanli et al., relied upon by the Office discloses an ELISA-like method for determining captopril in human blood using microtitre strips. The Office asserts that "[Jehanli et al.] describes the development of a sensitive, simple and rapid competitive ELISA assay for the determination of captopril (page 914)" for its *prima facie* obviousness support of a kit like that disclosed by the Applicants. *Id.* at 6. The authors, Jehanli et al., on the other hand, state that a "rapid" assay with their protocol requires four hours for completion. *See* Jehanli et al., p. 914. It may be true that such a system is considered rapid when compared to previous approaches using radiochemical methods, gas chromatography, gas chromatography-mass

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spectroscopy and high performance liquid chromatography, but none, including Jehanli et al., are acceptable approaches for a quick out-of-lab test for the presence of a drug. The Applicants' invention provides a system that allows results within 5 to 60 minutes. *See* Specification at 4. This is entirely unlike other disclosures because even at its slowest test time, a result can be determined in 25 percent of the time required by the teaching of, for example, Jehanli et al. During the course of patient treatment, that time difference is critical.

Second, the protocol disclosed by Jehanli et al. requires several technical wash steps and additional equipment, such as orbital shakers, making it further unsuitable for use outside a laboratory setting. *See* Jehanli et al. at 915. "The kit according to the invention [herein, meanwhile,] has the advantage that it can be used by an unskilled person for self-monitoring of a drug in a biological sample, *i.e.*, urine, blood or saliva, easily without the aid of any additional instrumentation." *See* Specification at 4. From the standpoint of obviousness, Jehanli et al. discloses a system with components and steps different from those disclosed by the Applicants. Additionally, there is no teaching or suggestion to modify Jehanli et al. in a way to achieve the kit or method disclosed by the Applicants.

Lastly, Jehanli et al. disclose a system that requires the use of enzymes. Such as system is less amenable to day-to-day conditions that would be encountered with use by hospital personnel or patients alike due to the instability of the enzymes themselves. *See* Jehanli et al. at 915. Jehanli et al. does not teach or suggest alternatives to enzymes as detection material either. Thus, even if Jehanli et al. were similar in all other respects (which, as noted above, it is not), it would not be similar to the method disclosed by the Applicants in that the test could typically be

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performed at ambient temperature. *See* Specification at 4. Consequently, the Applicants invention should be considered far more durable and practical than that disclosed by the art.

With respect to Baker et al., the Office states that "one would have a reasonable expectation of success by incorporating the ACE drug lisinopril, when the prior art already teaches the determination of another ACE related drug which has similar functions and using an antibody labeled with gold material, into the device and method of Jehanli et al., who already teach using the labeled antibodies to qualitatively or quantitatively determine the presence of a drug in a biological fluid." Office Action, 06/24/03 at 9. This fails to satisfy the *prima facie* case of obviousness.

The Office provides no support for the assertion that one drug can be substituted for another in a kit like that disclosed by the Applicants with a reasonable expectation of success simply because it shares a common functionality, i.e., agiotensin-converting enzyme inhibitor. *See Id.*, at 6-7. Moreover, drug structures can differ dramatically between the class of ACE inhibitors. Such structure can be expected to alter the compounds physical properties, reactivity, and interactivity. Consequently, Baker et al., while disclosing that lisinopril is an ACE inhibitor, like captopril, does not teach or suggest that all ACE inhibitors are interchangeable for a system as disclosed by the Applicant. Baker et al., col. 15, ll. 48-61. And since Jehanli et al. only teach the use of captopril and "do not teach the use of lisinopril," the Office cannot make its *prima facie* case of obviousness. Office Action, 06/24/03 at 7.

Finally, the Office cites Cole et al. for the proposition that a "labeled component can be an antibody labeled with metal particles such as gold sol particles . . . ." *Id.* at 8. The method of Cole et al., published in 1989, provides an immunoassay very different from that disclosed by the

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Applicants. It describes a system that a (a) monodispersed labeled component, (b) a stable suspension of a solid phase component, (c) a mixed aqueous suspension of said components, (d) an incubation time for binding, (e) a collection step, and then (f) a detection stage. Cole et al. teach a suspension method that is relatively labor, time and equipment intensive. Likewise, one skilled in the art would not look to Cole et al. to teach a substitute for enzymes in drug detection assays. In fact, Jehanli et al., who published seven years later (1996) and who sought a more rapid drug detection system, over what was known and practiced in the art did not mention the use of gold sol particle as a substitute from an enzyme-based approach to providing a rapid drug-detection assay. Similarly, there was no motivation to combine the references of Jehanli et al. and Cole et al. Lastly, colloidal gold is not disclosed by Cole et al.

Applicants assert that the Office failed to establish a *prima facie* case of obviousness for at least the reasons stated above. Accordingly, Applicants respectfully request the rejection of claims 1-3, 5-10, 12 and 14-21 be withdrawn.

The Office rejected claim 4 under 35 U.S.C. § 103(a) as being "unpatentable over Jehanli et al., (1996) Baker et al., and Cole et al., (US Patent 4,589,612) further in view of de Jaeger et al., (US Patent 4,837,168)." *Id* at 10, ¶ 14. According to the Office, de Jaeger et al. teach a method of qualitatively or quantitatively determining a component of a complex formed between at least one specific binding agent and its corresponding bindable substance. *Id.* Specifically, the Office cites Example 1 of de Jaeger et al. as disclosing latex bound antibodies. While this reference discloses the use of latex particles, it does not disclose the use of such particles in a method disclosed by the Applicants. For instance, the Applicants provide an invention where a drug in a biological fluid competes with a drug immobilized on the first part.

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Moreover, de Jaeger et al. relates to methods of qualitatively or quantitatively determining a component of a complex formed between at least one specific binding protein and its corresponding bindable substance which comprises labeling at least one component of said complex with a marker consisting of colorable latex particles. Thus, the component to be qualitatively or quantitatively determined in Jaeger et al. is a component of a complex formed between a binding protein and a bindable substance. In accordance with the present invention it is a drug, not a component of a complex, that is to be detected. The drug should further be present in a biological fluid. As stated above, the detection of the drug in accordance with the present invention is conducted by means of a competition between the drug in the biological fluid and the drug conjugate immobilized on the first part.

Applicants respectfully request that the rejection to claim 4 under 35 U.S.C. § 103(a) be withdrawn in light of the deficiencies noted in the references for the *prima facie* case for obviousness for claims 1-3, 5-10, 12 and 14-21 combined with de Jaeger et al.

Finally, the Office rejected claims 11 and 13 under 35 U.S.C. § 103(a) as being unpatentable over Jehanli et al., (1996), Baker et al., and Cole et al. (US Patent 4,589,612) in further view of Esser.

According to the Office, "it would have been obvious to modify the medical kit for qualitative or quantitative determination of a drug in a biological fluid comprising a first part coated with a drug conjugate and a second part that contains a labeled antibody and is adapted for receiving said fluid as taught by Jehanli et al., and Cole et al., to further incorporate the shape and material used in NUNC-IMMUNO™ STICK test system." *Id* at 12.

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As stated above, the deficiencies in Jehanli et al. and Cole et al. are not cured by Esser. The above arguments apply here. Accordingly, Applicants respectfully request that the rejection to claims 11 and 13 be withdrawn.

Esser discloses NUNC-IMMUNO™ STICKS where enzymes are used as label on the antibodies. As stated above the problem to be solved by the present invention is the provision of a kit and a method which allow the rapid and simple determination of drug levels in a biological fluid. The kit and method of the invention provide very distinct results, when used, in view of the fact that the anti-drug antibody is labeled with gold material or latex particles.

The kit and method according to the invention herein may be used at ambient temperature in view of the fact that the patient can use the kit by herself at home without the aid of any additional instrumentation. Enzymes being used in Esser's article are sensitive to for example, temperature fluctuations. When using enzymes as label a further substrate is further usually needed to be added in order for the color formation to develop, i.e., a further step making the test more complicated. A kit with enzymes would not be a possible alternative to the kit of the present invention where gold material or latex particles are used as labels on the antibodies.

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

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Respectfully submitted,

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